Structural deterioration of the Freestyle aortic valve: Mode of presentation and mechanisms

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Background: Structural valve deterioration is the major cause of bioprosthetic valve failure. Because of the unique design features and anti-calcification treatment of the Freestyle (Medtronic Inc, Minneapolis, Minn) stentless bioprosthesis, development of structural valve deterioration may differ in comparison with other bioprosthetic valves. This study evaluates the mechanisms and clinical presentation of structural valve deterioration in the Freestyle stentless bioprosthesis.

Methods: Between January 1993 and August 2005, 608 patients underwent aortic valve replacement with a Freestyle stentless bioprosthesis. The implantation technique was subcoronary in 475 patients and a root replacement in 133 patients. Mean overall follow-up was 5.6 ± 3.4 years. Follow-up was complete in all patients. Clinical and echocardiographic follow-ups were conducted prospectively.

Results: Freedom from structural valve deterioration was 95.8% at 10 years. Twelve patients showed evidence of structural valve deterioration and underwent reoperation for aortic regurgitation (n = 10) or aortic stenosis (n = 2). The mean age of patients with structural valve deterioration was significantly lower than patients without structural valve deterioration (62.6 ± 8.2 years vs 68.6 ± 8.3 years, P = .02). The median time between implantation and explantation was 8.7 years (range: 1.9-13.3 years). Eleven structural valve deteriorations occurred after subcoronary implantation, and 1 structural valve deterioration occurred after root implantation (P = .4). The mechanisms of structural valve deterioration were leaflet tears in 10 patients (6 in the left coronary cusp and 4 in the right coronary cusp), severe valve calcification in 1 patient, and cusp fibrosis in 1 patient. The interval between onset of symptoms and reoperation was acute or subacute in 10 patients.

Conclusion: At 10 years, the Freestyle stentless bioprosthesis shows excellent freedom from structural valve deterioration. Structural valve deterioration in the Freestyle stentless bioprosthesis relates to leaflet tear with minimal calcification in the majority of cases. Because of the fast onset of symptoms with leaflet tear, patients with a Freestyle stentless bioprosthesis should be informed of the preferential mode of failure and time-frame of symptoms.

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Replacement of a diseased aortic valve with a stented bioprosthesis is a well-established therapeutic approach. However, prosthesis degeneration ultimately limits the use of these devices, especially in younger patients. During the past decade, stentless aortic bioprostheses have been used for the replacement of diseased aortic valves and root pathologies. Excellent hemodynamic performance with early regression of left ventricular hypertrophy has been reported after implantation of stentless aortic valves.[1-3] The Freestyle (Medtronic Inc, Minneapolis, Minn) aortic root stentless bioprosthesis (FSB) may be implanted using different techniques, mainly in a subcoronary or root configuration. Since the first human implants in 1992, issues regarding durability have yet to be addressed.

Abbreviations and Acronyms
FSB = Freestyle aortic root stentless bioprosthesis
SVD = structural valve deterioration

Because of the unique design features of stentless valves, mechanisms and rate of failure may differ compared with various stented prostheses. Furthermore, mechanisms of failure may differ according to the implantation technique. The purpose of the present study is to describe the presentation, rate, and mechanisms of structural valve deterioration (SVD) in the FSB.

Patients and Methods

Between January 1993 and August 2005, 3428 prosthetic aortic valves were implanted in patients at the Québec Heart Institute, Québec City, Canada. Of these replacements, 608 were performed with an FSB. Table 1 summarizes the clinical and operative characteristics of the FSB cohort. During the same time-frame, 93 stented bioprostheses were explanted. Of these, 48 valves were explanted for SVD 10.9 ± 3.9 years after the initial procedure; prostheses were macroscopically calcified in 39.6% of cases with aortic regurgitation leading to reoperation in 64.3% of cases.

Among the 608 patients with an FSB, the implant technique was a subcoronary position in 475 patients (78.1%) and a root technique in 133 patients (21.9%). The operative techniques have been described.[4] The subcoronary implantation technique was performed with preservation of the noncoronary sinus.

All patients were followed annually in a dedicated valve clinic. Transthoracic echocardiograms were obtained every other year. Follow-up was complete in all patients. Mean overall follow-up was 5.6 ± 3.4 years (range 0.2-12.2 years) and 6.0 ± 3.3 and 4.0 ± 3.2 years for patients with subcoronary and root implantation configurations, respectively.

In accordance with the American Association for Thoracic Surgery and the Society of Thoracic Surgeons Committee for standardizing prosthetic heart valve morbidity,[5] SVD was defined as any change in function of an FSB resulting from any valve abnormality exclusive of infection or thrombosis.

Data Analysis

The primary end point was the presence of significant SVD of the FSB diagnosed on successive echocardiograms or at reoperation. Continuous data are presented as mean ± standard deviation. Percentages were determined for categoric variables. Continuous data were compared using a nonpaired Student *t* test, and categoric variables were compared using a chi-square analysis. By using univariate and multivariate analyses, perioperative risk factors age ≥65 years or <65 years, sex, presence of high blood pressure, and technique of implantation (subcoronary vs root) were evaluated to determine whether any single variable influenced the incidence of SVD. Time-related analysis was performed by the Kaplan-Meier method. A log-rank test was used to test for differences in freedom from SVD.

TABLE 1. Clinical and operative characteristics of the 608 patients with Freestyle (Medtronic Inc, Minneapolis, Minn) aortic valve bioprotheses

	n	%
Sex		
Male	334	54.9
Female	274	45.1
Age (y)	68 ± 8.3	
Cause		
Senile calcification	324	53.3
Bicuspid	152	25.0
Rheumatic	38	6.2
Myxomatous	31	5.1
Prosthetic dysfunction	30	4.9
Endocarditis	9	1.5
Other	24	3.8
Valve size distribution		
19 mm	17	2.8
21 mm	92	15.1
23 mm	153	25.2
25 mm	169	27.8
27 mm	149	24.5
29 mm	28	4.6
Operative technique		
Subcoronary	475	78.1
Root	133	21.9

Actuarial freedom from SVD was also stratified according to implantation technique and age.

Results

Clinical and Operative Profile

Twenty-seven patients (4.4%) within the FSB cohort required reoperation, 12 (44%) of whom had an SVD diagnosis. Fifteen other patients had their FSB explanted during the same period: early (<24 hours) in 4 patients because of technical issues and late (>3 months) in 11 patients because of severe mismatch (3 patients), endocarditis (2 patients), paravalvular leak (3 patients), partial dehiscence of root replacement (2 patients), and central regurgitation caused by sinotubular junction dilatation (1 patient). All patients with significant clinical or echocardiographic signs of SVD underwent reoperation. The mean age of patients with SVD was significantly lower than that of other patients (62.6 ± 8.2 years vs 68.6 ± 8.3 years, $P < .02$).

Table 2 depicts patient demographics and operative data at the initial operation for the 12 patients with SVD. Eleven patients with a subcoronary implant and 1 patient with total root implantation required reoperation for SVD. However, when considering the overall incidence of SVD according to the implantation technique, SVD was diagnosed in 2.3% of patients with a subcoronary implant and in 0.7% of patients with a root implantation ($P = .4$). The mean interval time

TABLE 2. Demographics and operative data at the initial operation in patients with structural valve deterioration

ID	Sex	Age at initial implant	Indication	FSB size (mm)	Type of procedure	Concomitant surgery
1	F	48	AR	25	Root	
2	M	55	AS	27	Subcoronary	
3	M	62	AS	25	Subcoronary	CABG × 1
4	M	68	AS	27	Subcoronary	
5	M	76	AS	27	Subcoronary	CABG × 1
6	F	68	AS	21	Subcoronary	
7	M	50	AR	27	Subcoronary	
8	M	67	AS	25	Subcoronary	CABG × 1
9	M	67	AS	27	Subcoronary	
10	F	60	AS	25	Subcoronary	
11	M	57	AS	25	Subcoronary	CABG × 1
12	M	65	AS	25	Subcoronary	CABG × 2

AR, Aortic regurgitation; *AS*, aortic stenosis; *FSB*, Freestyle (Medtronic Inc, Minneapolis, Minn) aortic root stentless bioprosthesis; *CABG*, coronary artery bypass grafting.

between FSB implantation and explantation for SVD was 7.8 ± 3.3 years (median: 8.7 years, range 1.9-13.3 years). In 3 patients, the interval between the initial procedure and the reoperation was within 5 years. One patient presented with a rapidly evolving calcific stenosis. In the other 2 patients, leaflet tears supervened on valves with no or minimal aortic regurgitation on previous echocardiography assessment.

Table 3 depicts clinical and operative variables of patients with SVD at reoperation. All patients presented dyspnea either secondary to severe aortic regurgitation in 10 cases or aortic stenosis in 2 cases. The interval between onset of symptoms and reoperation was acute (<1 month) or subacute (1-3 months) in 10 patients, and chronic (>3 months) in 2 patients.

Reoperation and Pathologic Findings

Ten patients with severe aortic regurgitation were found to have tears in 1 aortic cusp: 6 in the left coronary leaflet and 4 in the right coronary leaflet. Tears were located at the base (n = 4) or in the vicinity of the commissure (n = 6). Macroscopic calcification was absent in the 10 patients with aortic regurgitation caused by leaflet tear. In the 2 patients with aortic stenosis, severe leaflet calcification was found in 1 patient, and leaflet fibrosis with mild to moderate calcification was found in 1 patient. On histology, all leaflets showed different degrees of degeneration with the presence of fibrotic patches. Radiographic reports of explanted valve specimens were obtained through the Medtronic Heart Valve Laboratory (Santa Ana, Calif) in 10 patients. Reports depicted severe calcification in the 2 patients with aortic

TABLE 3. Clinical presentation and operative data performed during reoperation for structural valve deterioration

ID	Clinical presentation	Indication	Implant duration (y)	Operative findings	Calcification	AVR valve type	Size	Concomitant surgery
1	A	AR	12	Tear	Absent	St Jude (St Jude Medical, St Paul, Minn)	21	
2	S-A	AR	8, 8	Tear	Trace	St Jude	23	MVR
3	A	AR	6, 9	Tear	Absent	CE pericardial	21	
4	S-A	AR	8, 7	Tear	Trace	Magna	23	CABG × 1
5	A	AR	3, 3	Tear	Absent	Mosaic	29	
6	S-A	AR	8, 6	Tear	Trace	Magna	19	CABG × 1
7	S-A	AR	1, 9	Tear	Absent	St Jude	25	
8	A	AR	13, 2	Tear	Trace	CE pericardial	21	
9	S-A	AR	8, 3	Tear	Trace	Magna	21	CABG × 2
10	C	AS	3, 5	Stenosis	Severe	Magna	19	
11	C	AS	10, 2	Stenosis	Severe + fibrosis	Magna	19	CABG × 1
12	S-A	AR	11, 6	Tear	Trace	Mosaic	23	CABG × 2

A, Acute (<1 mo); *S-A*, subacute (1-3 mo); *C*, chronic (>3 months); *AR*, aortic regurgitation; *AS*, aortic stenosis; *CE*, Carpentier-Edwards (Irvine, Calif); *AVR*, aortic valve replacement; *MVR*, mitral valve replacement; *CABG*, coronary artery bypass grafting.

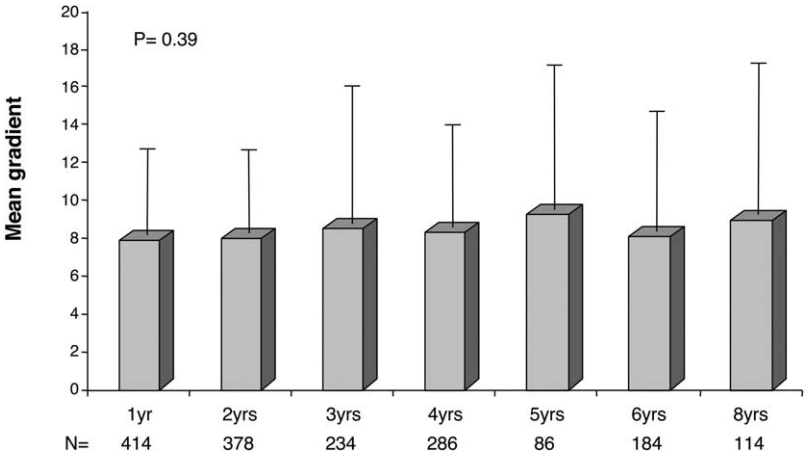

Figure 1. Mean gradient at echocardiographic follow-up for the 608 patients with Freestyle (Medtronic Inc, Minneapolis, Minn) valves.

stenosis, minimal calcification in at least 1 of the leaflets in 6 patients, and no calcification in 2 patients. Analysis could not take into account the anatomic position of the leaflet. One patient died perioperatively of a pulmonary embolism on the eighth postoperative day.

Freedom from Reoperation for Structural Valve Deterioration

Figures 1 and 2 show the echocardiographic follow-up in terms of mean gradient and aortic regurgitation grade for the whole FSB cohort. Actuarial freedom from reoperation for SVD in the FSB cohort was 95.8% at 10 years (Figure 3). Actuarial freedom from SVD stratified according to age (<65 years and ≥65 years old) was 96.1% and 95.3%, respectively. Univariate analysis did not identify gender, systemic hypertension, or chronic renal failure as risk factors for SVD.

Discussion

The FSB has been proposed to provide enhanced physiologic hemodynamic performance and potentially greater durability because of lower mechanical stress on the leaflets. The present study confirms the excellent midterm durability of the FSB. The longitudinal echocardiographic data further support the stability of the FSB performance at midterm. The current data compare favorably with the freedom from structural valve deterioration observed with currently available stented bioprostheses.[6-8] Bach and colleagues,[9] in a multicenter study, reported a similar freedom from structural valve deterioration in patients with an FSB.

Structural valve deterioration of bioprosthetic valves is a complex process that remains to be fully understood. Calcification is the most frequent factor contributing to the failure of contemporary glutaraldehyde-pretreated porcine aortic valve bioprostheses. Inflammatory and immune responses have been implicated in the calcification process of bioprosthetic valves.[10,11] To lessen the calcium deposits on glutaraldehyde-pretreated bioprostheses, several types of tissue anti-mineralization treatments have been proposed. The FSB is a porcine aortic root pretreated with alpha-amino oleic acid, an anti-calcification agent shown to abolish porcine leaflet calcifica-

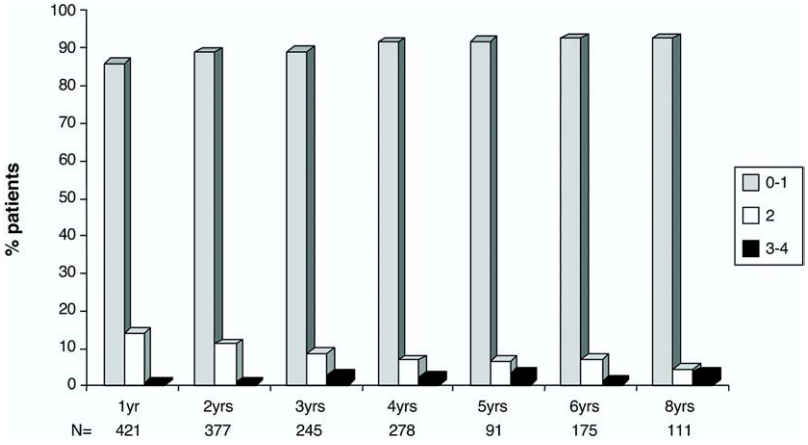

Figure 2. Longitudinal assessment of the echocardiographic aortic regurgitation grade for the 608 patients with Freestyle valves. *AI*, Aortic insufficiency.

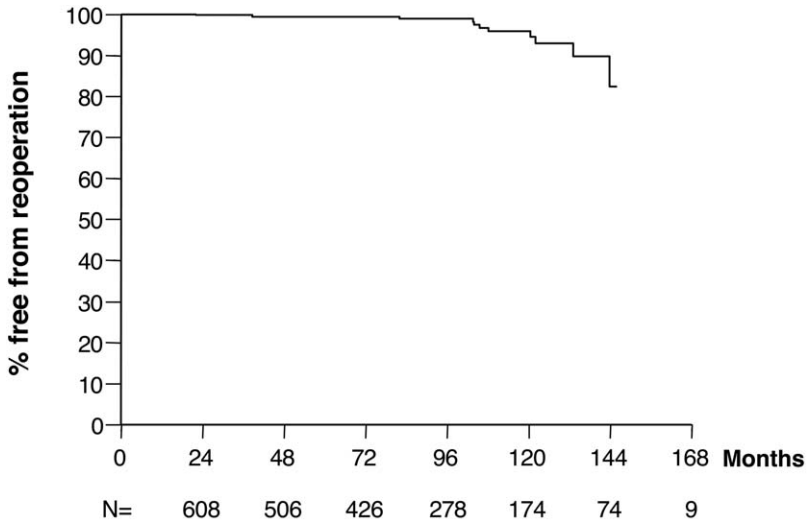

Figure 3. Actuarial freedom from reoperation for SVD in the 608 patients with Freestyle valves.

tion in animal models.[12] The current data support the anticalcification properties of the FSB valve because only 1 valve showed significant macroscopic calcium deposits. Mechanisms of valve deterioration were related to leaflet tear in 10 patients. Such a mechanism may suggest a "wear and tear" pathophysiology to explain the tears. The "wear and tear" phenomenon leading to valve failure has been reported with stented bioprostheses such as the Ionescu-Shiley bovine pericardial bioprosthesis[13] and is further supported by the subanalysis of our non-FSB cohort requiring reoperation for SVD. A recent multicenter study also suggested leaflet tear as the mechanism of valve failure in patients with an FSB.[9] Within the present study, the "wear and tear" hypothesis is substantiated by the histology of the explanted leaflets, which show variable amounts of degeneration of the extracellular matrix with minimal calcification. The leaflet tears were located on the right and left cusps, thus sparing the noncoronary cusp. Such a finding may imply an uneven stress distribution on the leaflets with premature degeneration of the overpressurized leaflets leading to leaflet tear. Because our preferred method of implantation for the subcoronary position includes preservation of the noncoronary sinus, one may speculate that suture placement in the right and left sinuses may confer uneven stress zones on the right and left leaflets leading to leaflet tear. Unfortunately, our histology examination did not differentiate between the leaflets' location, which could have further validated this hypothesis. On the other hand, the root implantation technique may lessen the uneven stress distribution secondary to sinus suture placement. Although no significant difference in the incidence of SVD was observed compared with the subcoronary technique, the only leaflet tear encountered in the root implantation group supervened more than 13 years postoperatively. Increasing the number of structural valve failures with a longer follow-up will establish whether differences in incidence of SVD may be linked to the implantation technique.

When assessing the clinical characteristics of patients sustaining SVD, our study shows a majority of patients with rapid onset of dyspnea as suggested by the interval of less than 3 months between symptom onset and reoperation. Such a clinical presentation suggests a rapid transition between a normal functioning valve and severe valve regurgitation caused by leaflet tear. This rapid transition is further supported by the stability of the aortic regurgitation in the FSB cohort at midterm.

Conclusion

The FSB shows excellent freedom from structural valve dysfunction at 10 years. Most SVD in patients with an FSB is linked to leaflet tear with minimal cusp calcification. Further investigations are required to thoroughly understand mechanisms implicated in SVD in patients with an FSB, such as the impact of the implantation technique. Finally, physicians should inform patients with an FSB on its preferential failure mode and the time-frame of symptoms associated with SVD in patients with an FSB.

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